PUBLIC HEALTH GUIDELINES

HIV infection screening in France

Laboratory tests and algorithms

CONCLUSIONS

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The guidelines and summary of this evaluation are available for download at www.has-sante.fr

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PREFACE: These conclusions form the first part of the public health guidelines on HIV infection screening, drafted by the Haute Autorité de Santé at the request of the Directorate General for Health. They relate to the methods for carrying out HIV infection screening tests. A second part will deal with the relevance of developing screening strategies and the screening programme in France. While the division made has attempted in particular to meet the specific expectations expressed about the issue of rapid screening tests, the technological approach to the screening tests and the methods for carrying them out cannot be separated from the more general strategic framework for HIV infection screening.

These conclusions include, on the one hand, guidelines on the methods for HIV infection screening and laboratory diagnosis in adults and children aged over 18 months and, on the other hand, guidelines and guidance on the role of rapid screening tests as part of the strategies for HIV infection screening and laboratory diagnosis.

DEFINITIONS OF TERMS USED

Screening analysis: the aim of the screening analysis is to demonstrate the presence of anti-HIV-1 and anti-HIV-2 antibodies, along with the presence of the p24 antigen for certain reagents.

Confirmation analysis: the aim of the confirmation analysis is to eliminate false positive results from the screening analysis.

Combined ELISA test: an ELISA test is said to be combined when it permits the simultaneous detection of anti-HIV-1 and anti-HIV-2 antibodies together with the p24 antigen.

Rapid screening test: a rapid screening test (RST) is a single test, interpreted subjectively, easy to perform and designed to give a result within a short period of time (usually less than 30 minutes) when it is performed on the patient. It can be carried out using whole blood, plasma or serum, depending on the matrix/matrices required by the manufacturer for its product. It is used to detect anti-HIV-1 and anti-HIV-2 antibodies.

Auto-test: an auto-test is a screening test where the sample is taken and the results are read and interpreted by the actual individual concerned.
Guidelines on HIV testing and laboratory diagnosis

These guidelines relate to the methods used for HIV infection screening and laboratory diagnosis in adults and children aged over 18 months, with the exception of the screening of blood donations and of organ and tissue donors. They do not apply to rapid screening tests (RST), for which specific guidelines are described in detail in the following section.

General principles

The laboratory diagnosis of the HIV infection is based on a two-stage strategy: a screening analysis followed by a confirmation analysis. A positive screening analysis must always be supplemented by a confirmation analysis on the same sample. An HIV infection can only be confirmed when the result of the confirmation analysis is positive and consistent results are obtained for two separate samples.

The prescribing doctor is recommended to provide the laboratory specialist with the clinical information supporting\(^1\) the diagnostic guidance.

Should one rather than two techniques be used for screening analysis?

Continuing to use two screening techniques on the same sample when carrying out a screening analysis for anti-HIV antibodies is no longer justified in 2008.

This change to current practice is based on an analysis of the performance achieved by the techniques currently available on the European market for HIV infection screening, as well as on a comparison of the performances of the strategies based on one or two screening techniques.

Choosing the screening analysis technique

Laboratory specialists performing the diagnosis of the HIV infection in the lab must use, as part of the screening analysis, a CE-marked combined ELISA test with a p24 Ag detection threshold at least equivalent to the minimum threshold required by the current European legislation applicable to p24 Ag detection tests\(^2\).

If the screening analysis gives a negative result, this indicates the absence of any HIV infection, except if the patient is suspected of having been exposed to HIV within less than 6 weeks prior to this (see below).

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\(^1\) Especially age, a suspected primary infection, specific pathological situations (cases of co-infection, associated treatments etc.).

\(^2\) In 2008 this threshold has been set at 50 pg/ml of HIV Ag.
Choosing the technique to use as part of the confirmation analysis and differentiation between HIV-1 and HIV-2 infections

The technique used as part of the confirmation analysis for an HIV-1 infection remains the Western blot (WB) or immunoblot (IB). The WB interpretation criteria for HIV are unchanged (criteria were defined according to the Anaes guidelines in 2000 and by the WHO) and are included in the appendix to this document.

It is recommended to differentiate between the infections caused by HIV-1 and HIV-2 respectively, due to pathogenic differences between the two types of virus, HIV-2’s natural resistance to certain antiretroviral drugs and to the absence of off-the-shelf tests for quantifying the plasma HIV-2 RNA.

The confirmation analysis must therefore help ascertain whether an HIV infection is present or not, while also differentiating between the HIV-1 and HIV-2 infections.

If the result of the WB or IB is negative or indeterminate, in order to avoid missing a primary infection during the pre-seroconversion stage, a test needs to be carried to reveal the virus’s components (detection of plasma viral RNA or p24 Ag with a detection threshold at least equivalent to that of the combined ELISA test used for the screening analysis, confirmed by a neutralisation test in the case of a positive result).

Confirmation of the HIV infection always requires the provision of consistent results from two separate samples.

If the screening analysis is positive, the confirmation analysis must be carried out on the initial sample. If the confirmation analysis is positive, a second sample must be taken and tested in order to eliminate any identity error. It is recommended to carry out a new screening analysis on this second sample (using the screening reagent used initially or a different one). A new confirmation analysis does not need to be carried out. Only a positive result with this second sample will be able to validate the result and confirm the diagnosis of an HIV infection.

Where problems arise in interpreting the results of these analyses, close consultation is recommended between the prescribing doctor and the laboratory specialist. Any atypical profile must be investigated using specific diagnostic techniques (specific serological tests for variants, viral isolation, genome detection tests etc.), especially if the clinical and/or epidemiological context is conducive to HIV exposure.

Issuing results

The test results must be issued in a confidential manner. With the patient’s consent, this task is first entrusted to a doctor during a specific consultation, enabling him or her to provide information about preventing HIV infection and, if an infection has been diagnosed, to start managing and monitoring the patient.

If a test has been carried out without any prescription, at the patient’s explicit request (i.e. outside the current regulatory framework), it is up to the actual laboratory specialist to inform the patient. The result must be issued during a discussion where the laboratory specialist advises the patient to contact his or her primary care physician. In the case of a positive result where there is no primary care physician involved, the laboratory specialist must offer support to the patient and can, in particular, direct the latter to a hospital-community network or any of the regional anti-HIV coordination centres (COREVIH).
These guidelines imply an upgrade to the current regulatory framework (1 October 2008). Furthermore, shifting from a strategy based on the use of two screening analysis techniques to a strategy based on the use of a single technique will result in modification of the Nomenclature of Procedures in Laboratory Medicines in terms of the procedure’s description and rating.

**Duration of serological follow-up in the case of suspected HIV exposure**

Based on the performance of the techniques currently available on the European market, a negative result from the combined ELISA screening test 6 weeks after suspected HIV exposure will be considered as indicating that no HIV infection is present. In the case of post-exposure prophylaxis, the period remains 3 months after discontinuing treatment.

**Screening and laboratory diagnosis strategy in the case of suspected HIV infection within less than 6 weeks and without any prophylactic treatment**

An initial search for the HIV infection must be carried out in the exposed patient from the very first consultation, using the methods previously defined. It will be repeated 6 weeks after the time of suspected HIV exposure.

**Screening and laboratory diagnosis strategy in the case of suspected HIV infection and with prophylactic treatment**

An initial search for the HIV infection must be carried out in the exposed patient from the very first consultation, using the methods previously defined. It will be repeated 1 month and 3 months after discontinuing the prophylactic treatment. A negative result from the combined ELISA screening test 3 months after discontinuation of prophylactic treatment will be considered as indicating that no HIV infection is present.
TESTING ALGORITHM
GENERAL CASE
ADULTS AND CHILDREN AGED OVER 18 MONTHS

Search for anti-HIV-1 and HIV-2 AB and p24 Ag using a combined test

- No infection present*

+ WB or IB Differentiation HIV-1/ HIV-2

- or indeterminate

Search for anti-HIV-1 and HIV-2 AB and p24 Ag using a combined test (2nd sample) **

- HIV infection confirmed

+ Identification error

Search for plasma HIV RNA or p24 Ag

- Primary infection

+ Serological check

- No infection Probable non-specific reaction £

+ Serological check

- Serological check Additional investigations if variants suspected

* unless suspected HIV exposure within the previous 6 weeks

$ 1 to 2 weeks later

£ To be interpreted according to clinical context

+: positive result

-: negative result

AB: antibody

** The combined test carried out on the second sample may be identical or different from that carried out on the first sample.
Role of rapid screening tests in HIV infection screening and laboratory diagnosis strategies in France

These conclusions relate to the role of RSTs in HIV infection screening and laboratory diagnosis strategies, excluding auto-tests (which the National Ethics Advisory Committee and the National AIDS Council published concurring opinions on in November and December 2004).

A distinction should be made within these conclusions between those which are guidelines and those provided for guidance in anticipation of the results from the experiments planned to be carried out in France.

As part of these conclusions, a rapid screening test (RST) is defined as a single test, interpreted subjectively, easy to perform and designed to give a result within a short period of time (usually less than 30 minutes) when it is performed on the patient. It can be carried out using whole blood, saliva, serum and plasma, depending on the matrix/matrices required by the manufacturer for its product. It is used to detect anti-HIV-1 and anti-HIV-2 antibodies.

Initial considerations and general principles

Based on their current performance, acceptability and potential benefits, the RSTs available on the French market in 2008 and with CE marking offer a valuable tool to supplement the traditional screening model based on the use of ELISA tests, thereby helping achieve two main objectives:

- obtaining a rapid diagnosis in certain emergency situations so that appropriate management can be initiated
- facilitating access to knowledge about the serological status and to the options for preventive and therapeutic management of the HIV infection for certain groups of the population who have inadequate or even no access to the traditional screening system.

Following an analysis of the literature available and in agreement with the working group, guidelines have been drawn up on the use of RSTs in certain medical emergency situations. However, difficulties with the transposition of the results from the studies that have primarily been carried out in the US, the limitations of these studies and the lack of epidemiological data in France making it possible to characterise the target populations have meant that guidelines could not be drawn up straightaway on the use of RSTs with a view to reducing the obstacles to screening. In view of the RSTs’ potential valuable role in facilitating access to screening in both a medical and non-medical context, guidance is offered, calling for projects to be implemented involving a structured evaluation in order to confirm the expected benefits in France.

No matter the circumstances in which RSTs are used, two general principles stipulated as part of conventional HIV infection screening are applied in the same way to RSTs:

1) an RST can only be carried out with the informed consent of the person being offered the screening.

3 Except in life-threatening emergencies where the person is unable to give their consent.
2) an RST can only be carried out in accordance with the general conditions of use which are subject to the specific guidelines indicated below, especially after a quality assurance system has been introduced.

**Guidelines on the use of RSTs in medical emergency situations**

It may be useful for an RST to be carried out on whole blood or serum/plasma (according to local conditions) by a healthcare professional working in a healthcare provision centre (emergency department, hospital unit, maternity ward etc.) in the following emergency situations, after obtaining the informed consent of the person affected:

- **Accident involving occupational exposure to blood**: an RST may be offered to the source patient.
- **Accident involving sexual exposure**: an RST may be offered to both partners in the emergency department or as part of the systems for managing accidents involving exposure to biological fluids.
- **Childbirth involving pregnant women whose HIV serological status is unknown or pregnant women who have had suspected HIV exposure since the last screening test was carried out during their pregnancy**: an RST may be offered to the pregnant woman.
- **Diagnostic emergency due to the occurrence of an acute pathology suggesting the AIDS stage**: an RST may be offered to the patient.

In all these cases, a combined ELISA test will have to be carried out as quickly as possible, whatever the results of the RST.

**Guidance on the use of RSTs in populations inadequately covered by the traditional screening model**

The use of RSTs may be suggested in order to:

- facilitate access to screening for populations which have inadequate access to the current system in relation to their risk exposure for a variety of reasons (in particular, populations which avoid institutions, are marginalised, are outside the healthcare system, have no entitlement to social security etc.)
- improve access to screening results.

This use can be provided for within traditional screening provision structures (free, anonymous screening centres (CDAG), centres for information, screening and diagnosis of STDs (CIDDIST) etc.) or within alternative structures. The RST can be offered using whole blood or saliva by healthcare professionals and other qualified persons. In every case, the use of RSTs must be included as part of a structured evaluation approach.

The use of RSTs should therefore be adopted as part of implementing projects. These projects will have to be based on hypotheses documented by their promoters and envisage a systematic evaluation approach. This evaluation will have to help confirm the expected benefits of using RSTs in the exact circumstances relating to each type of project and for the defined target populations, based on criteria adapted to the objectives being pursued.

The results of these evaluations will be instrumental in drawing up guidelines on those circumstances where RSTs are currently used in practice in France.
Guidelines on the general conditions for using RSTs

Implementing a quality assurance system.

In every case, the use of RSTs must be supported by the implementation of a quality assurance system in order to limit any risk of error when handling and interpreting these tests and to guarantee the quality of the results obtained. This system must systematically ensure:

- the initial verification of the qualifications of the staff entrusted with carrying out the RSTs and regular assessment of their skills
- the implementation of a training programme for staff carrying out RSTs
- guaranteed traceability of the RSTs used and their results
- access to a support network and medical care for any person who might receive a positive screening result.

It will be possible to adapt each of these elements according to the actual features of the relevant screening institutions.

The precise definition of a technical specification for implementing a quality assurance system in conjunction with the use of RSTs must be examined within a specific working group.

The current legal framework only permits blood or saliva samples to be taken by doctors and midwives or, when prescribed and using certain methods, by nurses and staff in medical analysis laboratories. The use of RSTs in institutions closest to the populations targeted by authorised non-healthcare professionals (association volunteers, social workers etc.) can only be envisaged within the projects described above.

Rapid screening algorithm

RST results should be interpreted taking into account the clinical and epidemiological context. A negative RST result can be considered as excluding any HIV infection, except if the patient has been recently exposed within less than three months. In this situation a new HIV serological test will have to be carried out using a combined ELISA test according to the general scheme defined in the previous guidelines.

Any positive RST result must be confirmed by a WB or IB, based on the scheme defined in these guidelines, in order to eliminate a false positive result.

In the case of an invalid result (uninterpretable RST), a combined ELISA test will need to be carried out according to the general algorithm defined in the previous guidelines.

Issuing the results of an RST

The results must be issued in the form of a “positive/negative search”. A standardised procedure must be provided for giving the results to the patient in the form of a signed written document (specifying the type of sample taken, the nature of the test and its name, the result and the limits of this result). The result of the screening test and its interpretation must be mentioned.
Information

The provision of suitable information must allow, in every case, at least to guarantee informed consent to the rapid screening test and the patient's understanding of the rapid screening process. Anyone taking an RST must be informed in particular that the results of the test may be given to them during the same visit. Above all, an explanation must be given about the meaning of a negative result, invalid result and positive result, and about the need, in the case of the latter result, to carry out a confirmation test involving a blood sample being taken at a medical institution.
**TESTING ALGORITHM FOR RST**

**ADULTS AND CHILDREN AGED OVER 18 MONTHS**

1. **Search for anti-HIV-1 and HIV-2 AB using an RST**
   - **-**
     - **No infection present***
   - **+**
     - **Search for anti-HIV-1 and HIV-2 AB and p24 Ag using a combined Elisa test**
       - **Invalid**
       - **Search for anti-HIV-1 and HIV-2 AB and p24 Ag using a combined Elisa test (2nd sample)**
         - **+**
           - **HIV infection confirmed**
             - **Identification error**
               - **Serological check**
               - **Serological check**
               - **Serological check**
         - **-**
           - **Primary infection probable\$ or variant or HIV-2**
             - **Serological check**
             - **Serological check**
             - **Serological check**
2. **Search for plasma HIV RNA or p24 Ag**
   - **+**
     - **No infection**
     - **Probable non-specific reaction**
     - **Serological check\$ Additional investigations if variants suspected**
   - **-**
     - **- or indeterminate**

* unless suspected HIV exposure within the previous 3 months or incidences of deep immunodepression or rare variants
\$ 1 to 2 weeks later
\$ To be interpreted according to clinical context
+ : positive result
- : negative result
AB : antibody
## Appendix. Interpretation criteria for HIV Western blot

<table>
<thead>
<tr>
<th>Anaes 2000 criteria for HIV-1</th>
<th>WHO criteria for HIV-2</th>
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<tbody>
<tr>
<td><strong>Certain positivity</strong></td>
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<tr>
<td>At least 2 anti-Env antibodies (anti-gp120 and anti-gp160)</td>
<td>At least 2 anti-Env antibodies (gp140, gp105/125, gp36) ± Pol bands (p34, p53, p68) and Gag bands (p16, p26, p56)</td>
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<tr>
<td>AND 1 anti-Gag or anti-Pol antibody</td>
<td></td>
</tr>
<tr>
<td><strong>Certain positivity</strong></td>
<td></td>
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<tr>
<td>a) 1 anti-p24 antibody</td>
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<tr>
<td>AND 1 anti-gp160 antibody</td>
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<td></td>
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<tr>
<td>b) 2 anti-Env antibodies (anti-gp120 and anti-gp160)</td>
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<tr>
<td><strong>Profiles to be checked</strong></td>
<td></td>
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<tr>
<td>Isolated anti-gp160 antibodies</td>
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<tr>
<td>Isolated anti-p24 antibodies (± anti-p55)</td>
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<tr>
<td>Isolated anti-p34 antibodies (± anti-p24)</td>
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<tr>
<td><strong>Negativity</strong></td>
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<tr>
<td>Anti-p17 antibody</td>
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<tr>
<td>Other profiles not considered</td>
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<tr>
<td>No antibodies</td>
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Participants

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This study was coordinated in the Economic Evaluation and Public Health Department by Dr Olivier SCEMAMA and Anne-Isabelle POULLIÉ, under the supervision of Catherine RUMEAU-PICHON. Document research and management were carried out by Aurélien DANCOISNE, researcher, and Laurence FRIGÈRE, assistant researcher. Secretarial services were provided by Sabrina MISSOUR.

Scientific societies and professional associations

The following scientific societies, professional associations and institutions were asked to participate in compiling these guidelines:

- ACT UP-PARIS
- Agence française de sécurité sanitaire des produits de santé (AFSSAPS)
- AIDES
- Association Des Epidémiologistes de Langue Française (ADELF)
- Collège des économistes de la santé (CES)
- Collège des Universitaires de Maladies Infectieuses et Tropicales (CMIT)
- Collège Français de Médecine Générale (CFMG)
- Collège National des Généralistes Enseignants (CNGE)
- Collège National des Gynécologues Obstétriciens Français (CNGOF)
- Collège National des Sages-Femmes (CNSF)
- Comité Consultatif National d’Éthique des sciences de la vie et de la santé (CCNE)
- Conseil National du Sida (CNS)
- Fédération nationale des associations des sages-femmes (FNASHF)
- Fédération Nationale des Collèges de Gynécologie Médicale (FNCGM)
- Institut National de Prévention et d’Education pour la santé (Inpes)
- Institut National de la Transfusion Sanguine (INTS)
- Institut de Veille Sanitaire (InVS)
- Sida Info Service (SIS)
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